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Transcatheter mitral valve repair and replacement

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Mitral regurgitation is the valvular heart disease with the highest prevalence in the Western countries, and its prevalence increases with age.¹ Conventional surgery provides excellent results in the younger population free of comorbidities, but up to 50% of the patients with severe mitral regurgitation are today denied surgery because of increased surgical risk.² During the last few years, transcatheter valve interventions have emerged as a therapeutic option to treat inoperable or high-risk patients who are not amenable for conventional open-heart surgery.³

Several surgical procedures have inspired transcatheter devices to treat mitral regurgitation, ranging from leaflet repair, annular and ventricular remodelling and valve replacement. Today, transcatheter edge-to-edge repair with the MitraClip system (Abbott Vascular Inc., Menlo Park, California, USA) is the most advanced technology available for clinical use, with proven safety, efficacy and durability in different clinical settings.³ In addition to the MitraClip system, different technologies with diversified approaches are today under development to improve the transcatheter mitral valve repair (TMVR) armamentarium.⁴ Transcatheter mitral valve implantation (TMVI) has recently become an option for those patients with previous open-heart surgery and a degenerated bioprosthesis or with recurrent mitral regurgitation following annuloplasty.⁵ Although transcatheter mitral implant in a native anatomy introduces a number of challenges, the feasibility of TMVI in human has been recently reported in high-risk patients with functional and degenerative aetiology. Five devices have been tested in clinical studies with variable outcomes (Fig. 1).

As replacement technologies are developed, it should be questioned whether TMVI should become the preferred transcatheter mitral valve therapy. TMVI promises several advantages. It has the potential to be more reproducible, applicable to many patients (one valve

for all), associated with predictable results and to be less technically demanding and easier to learn procedure. On the other hand, TMVR, although more technically challenging, may be associated with a superior safety profile, as compared with replacement, as it involves a less acute change in valve anatomy and physiology, does not involve a tissue implant and does not require anticoagulation.

As the future interventions are developing, it is difficult to predict which technology will prevail; however, it is not difficult to predict that there will be a role for both procedures, such as the case with surgery.






Previous clinical experiences from surgery

Although transcatheter interventions may act differently, surgical background can be the source of inspiration for the future.

In the early days of cardiac surgery, before heart–lung machine technology was established, several off-pump mitral repair techniques were attempted, mainly directed at annular remodelling. With the introduction of the open-heart approach and the development of artificial prostheses, repair disappeared progressively from the surgical arena. Surgeons preferred replacement because it is easier to perform and more predictable because of the more reproducible approach provided by valve replacement. However, in the late 1980s and early 1990s, mitral repair gained progressively more acceptance and became the gold standard treatment of mitral regurgitation due to a higher safety profile, both in terms of hospital mortality and long-term comorbidity and quality of life. The main limitation of mitral valve replacement is that the ideal replacement prosthesis should have the following characteristics: durability, easy and reproducible implant, absence of transvalvular gradient, absence of valve regurgitation, no risk of Left Ventricle Outflow Tract (LVOT) obstruction, no need for anticoagulation, no deterioration of left ventricular (LV) function, respect of LV physiology and blood flow pattern. In short, the ideal prosthesis does not exist.

Until the late 1990s, mitral repair was performed only by selected ‘dedicated’ physicians, who developed specific skills and expertise to deliver reliable outcomes in a variety of clinical and anatomical scenarios. Only recently, after more than 2 decades of surgical practice and strong educational efforts, mitral repair is performed by almost all high-volume cardiac surgeons, with

Fig. 1

	NeoVasc	CardiAQ	Tendyne/ Lutter	Edwards	Twelve
Valve name	Tiara	TMVI-TA, TMVI-TF	Tendyne TMVR	Fortis	Twelve
Device image					
Description	Ridge fixation	Leaflet and radial force fixation	Apical tether	Leaflet clipping	Barbs attachment and proprietary cork-effect
Access	TA	TA and TF	TA	TA	TA
Status*	• >10- patients	• 10 patients • Acquired by Edwards	• >20 pts • Acquired by Abbott	• >20 pts, trial stopped for thrombosis	• >5 patients • Acquired by Medtronic

Transcatheter mitral valves already implanted in humans.

standardized approach and reproducible outcomes. Valve replacement still plays a role, but as a second-line option, when repair efficacy and durability are questionable.

The current scenario may repeat now and in the near future in the field of transcatheter valve interventions: repair and replacement will be confronted with their strengths and limitations, and will very probably find a complementary role.

Surgical literature has shown that in patients with degenerative mitral regurgitation (DMR), valve repair, as compared with replacement, yields superior acute and long-term outcomes, both in terms of morbidity and mortality. Therefore, surgical mitral valve repair is the treatment of choice for patients with severe DMR, owing to its well documented advantages over mitral valve replacement in terms of morbidity and mortality.⁶

Effective and timely correction of DMR has a highly beneficial impact on the prognosis of patients and can even be associated with a life expectancy and a quality of life similar to those of the age-matched general population.⁷ The positive prognostic benefit of early intervention in young patients with DMR is lost when a prosthesis is implanted, due to the prosthesis-related morbidity and

mortality. Therefore, life expectancy of a patient with a prosthetic valve is reduced, mainly due to thromboembolic and haemorrhagic events and to the risk of prosthetic-related endocarditis.⁸ Thromboembolic complications are the most important cause of morbidity and mortality in patients with a prosthetic heart valve, with an estimated incidence of clinical events ranging from 0.6 to 2.3% per patient-year.⁹ The risk of thromboembolic complications is similar for patients with mechanical valves on warfarin therapy and bioprosthetic valves without warfarin therapy. Moreover, obstruction of a prosthetic valve may be caused by thrombus formation, pannus ingrowth or their combination. The incidence of obstructive valve thrombosis varies between 0.3 and 1.3% per patient-year in patients with mechanical valves.⁹ Haemorrhagic complications are another major concern related to long-term anticoagulation, with an annual risk of $\approx 1\%$ per patient-year.^{9,10} The incidence of prosthetic valve endocarditis is around 0.5% per patient-year, even with appropriate antibiotic prophylaxis. Prosthetic valve endocarditis is an extremely serious condition with high mortality rates (30–50%).¹¹

Superiority of mitral repair in the context of DMR has been demonstrated also in elderly patients.¹² In patients with high surgical risk, benefits of repair are even more

pronounced. TMVR cannot be applicable to all patients due to intrinsic anatomical limitations (e.g. calcified leaflets, advanced multisegment disease and large lesions requiring resections), but anatomical variability can also become a limitation for TMVI. As an example, most current technologies rely on native leaflet and subvalvular apparatus for fixation. Patients with advanced degenerative anatomical lesions may be suboptimal candidates for some replacement technologies.

Currently, the majority of the patients who undergo transcatheter mitral interventions are high-risk patients with functional mitral regurgitation (FMR). The benefits of surgical repair over replacement in patients with FMR are less clear compared with DMR patients.

Acker *et al.*¹³ in a large multicentre randomized trial compared mitral repair (undersized annuloplasty) and mitral replacement in 251 patients with severe ischaemic FMR. The authors did not observe any significant difference in LV reverse remodelling or survival at 12 months between patients who underwent mitral repair and those who underwent mitral replacement, apart from a higher recurrence in mitral regurgitation that was observed in the repair group. The conclusion was that replacement provided a more durable correction of mitral regurgitation, although this was not associated with any clinical impact. Although the study was not powered for mortality, the repair patients showed a trend to better early survival (30-day mortality almost three-fold higher in the replacement group 4% compared with repair group 1.5%). Indeed, although significant recurrent mitral regurgitation developed in more than 30% of the patients in the repair group, the patients in this group who did not have recurrent ischaemic mitral regurgitation realized a 22.6% reduction in LV volume versus a 6.8% reduction in the replacement group.

However, repair is not always effective, and patient selection is extremely important to prevent the recurrence of FMR. Anatomical predictors of repair failure should be taken into consideration when selecting patients for restrictive annuloplasty to obtain a durable repair.¹⁴

The current study suggests that particularly when treating FMR, repair can be beneficial even at the cost of a higher recurrence rate due to a superior safety profile. Safety will certainly play a central role in the future to further expand mitral interventions into the lower risk categories and to enable early treatment.

Mitral repair is also more suitable for an early indication approach to overcome the prosthesis-related complications. In addition, when repair is applied early in the course of the disease, the chance of effective mitral regurgitation reduction is higher. These data support the fact that if durable and effective mitral repair is performed, also in the context of FMR a transcatheter

repair approach could be beneficial compared with TMVI. TMVI should be preferred only in patients with low likelihood of durable repair.

The reasons for the superiority of repair compared with replacement in surgical experience finds a potential ground in mitral valve anatomy and physiology.

Mitral valve complex and physiology

We are used to refer to the mitral as a 'valve'. However, the mitral is not only a simple valve: the mitral is a 'complex' and should be considered as an integrated part of the LV. The mitral valve complex is composed by the leaflets, the annulus, the chordae, the papillary muscles, it is in continuity with the atrial wall and the aortic valve and plays a fundamental role in the demarcation of the inflow–outflow ventricular tracts.

In addition to the simple function of valve, ensuring unidirectional blood flow from left atrium to LV, the mitral complex has structural and haemodynamic functions too. Residual abnormalities of the heart structures after mitral replacement may compromise these functions. At least some of these abnormalities are related to the inherent properties of the valve substitute and might conceivably be avoided or minimized by a more physiological restoration, which is the aim of the mitral valve repair.

The mitral valve apparatus and the LV are integrated structures, connected by the chordae tendineae. The proximity, structural continuity, design characteristics and haemodynamic factors play an important role in providing essential 'crosstalk' to achieve optimal function of the mitral valve. Discontinuation of the structural contiguity of mitral apparatus and LV after mitral valve replacement results in LV maladaptive remodelling and worse performance. Moreover, mitral annulus is a three-dimensional dynamic structure, and its contraction plays an important role in the determination of the contractile function of the LV: the fixation of a prosthetic valve to the mitral annulus makes it a static structure and may lead to the reduction of the systolic contribution of the basal portion of the LV to the ejection. This may be an issue mainly in heart failure patients with reduced Ejection Fraction (EF).

In addition to the structural function, the mitral complex also plays an important haemodynamic role to direction the blood flow. As described by Yacoub and Cohn,¹⁵ the flow through the heart chambers is an integrated system that depends on a combination of patterns of flow in and out of the valves and implies a fluid–structure interaction. Imaging studies showed that in the LV inflow through the open mitral valve gives rise to recirculating flows beneath the valve leaflets, the dominant direction being under the free edge of the anterior mitral leaflet. Part of the blood volume is thus redirected towards

the outflow tract, according to a vortex-like pattern. Transient recirculation is also seen beneath the posterior mitral valve leaflet.^{16,17}

There is no doubt that such a complex interaction may be preserved only with a reparative approach, aimed to respect not only the anatomy, but also the physiology of the mitral complex. Circulation is based on 'dynamism and crosstalk', actions and reactions play a game the principle of which is the preservation of energy. Loss of the vortex-like circulation patterns means loss of energy, which might result in increased LV stress and less-efficient work.¹⁶

Access considerations

Although for TMVR, including edge-to-edge repair and direct annuloplasty, the transeptal access is widely used, access for TMVI still represents an issue. At the moment, TMVI requires a large and rigid sheath, and this aspect may affect the deliverability of the system, especially in case of long route. Deliverability, in fact, depends on the size of the delivery system, length of the device, rigidity, time to deploy and patient's haemodynamic at the moment of the deployment (including need and duration of rapid pacing).

At the moment, a transfemoral or transeptal approach may be challenging in TMVI because of the angulation and the deliverability of a large and rigid device across the septum.

Direct transatrial approach is a possible alternative, which has been used for mitral valve-in-ring procedures.¹⁸ However, direct transatrial approach has been almost abandoned because of the lack of coaxiality of this access within the mitral annulus.

Transapical approach represents so far the best route for TMVI, assuring by definition of optimal coaxiality. However, it should be considered that the LV wall in heart failure patients with mitral regurgitation is totally different from the LV wall of patients with aortic stenosis and hypertrophy. In mitral regurgitation patients, LV is usually thin, dilated, dysfunctional and arrhythmogenic. Therefore, apical access may represent an issue in patients undergoing TMVI, potentially causing acute LV dysfunction, EF worsening and haemodynamic problems. Moreover, extremely compromised patients with severely depressed EF may not tolerate transient hypotension during rapid pacing. Last but not least, a percutaneous approach is associated with faster recovery and less 'surgical stress' as compared with transapical. In the context of aortic stenosis, in which the treatment is associated with immediate improvement of haemodynamic, these factors may play a secondary role. But in the case of FMR treatment, in which mitral regurgitation treatment is associated with a transient increase in afterload, minimization of invasiveness may be key for the success of the procedures.

Technical open issues with transcatheter mitral valve implantation and transcatheter mitral valve repair

Proven that TMVI is feasible and that with improvement of the technologies it would increase its applicability, several open issues remain today regarding the performances of the device. One of the technical challenges of TMVI is the fixation of the prosthesis in mitral position. A fixation method relying solely on radial force is questionable: in patients with both DMR and FMR mitral annulus is usually dilated, so a very large device is required to obtain adequate radial force to allow proper fixation. However, the use of a large device may increase the risk of damage to the stent of the device, which may be fractured by the continuous movement of the LV in a high-pressure environment. Additional fixation elements, in addition to radial force, would be required to ensure proper fixation of the device to LV or to the other elements of the subvalvular apparatus. This is particularly important if we consider that one of the target of TMVI would be treat different causes with a single device: not only DMR and FMR are different; DMR include a wide spectrum of different pathological aspects, ranging from Barlow disease (in which the excess of tissue determines an excess of movement that could prevent optimal fixation) to fibroelastic deficiency with isolated segmental prolapse (in which the lack of tissue may not assure a landing zone for the device).

Adjunctive open issues to be considered regarding long-term performance of TMVI devices are the risk of leaflets damage and the risk of LVOT obstruction.

As repair technologies are concerned, several challenges should be addressed. First, due to a wide variability of potential lesions underlying mitral regurgitation, a series of different technologies should be available, and physicians dedicated to transcatheter mitral interventions should become expert in using more than one device if they want to address most potential patients. Currently, MitraClip has been a winning device also because it is versatile, and it can be used both in patients with FMR and DMR. However, MitraClip implantation is a procedure very different from other interventions. In addition to the transeptal puncture, the procedure is more a robotic 'surgical like' endovascular procedure, with free-floating navigation in a three-dimensional space. In addition, differently from most interventional procedures, MitraClip requires advanced three-dimensional echocardiographic guidance to achieve good results. Learning curve of MitraClip is longer than for Transcatheter Aortic Valve Implantation and requires a skill set that differs from that of a conventional interventional cardiologist or a cardiac surgeon. The same limitations and concerns apply to most repair technologies. From a technical standpoint, most repair technologies on the horizon require advanced and specific skills, which may limit the fast expansion of TMVR, as compared

with TVMI, in which reproducibility can be higher and learning curve may be shorter.¹⁹

Some technologies for TMVR are easier to perform, such as coronary sinus annuloplasty. However, as they are based on unproven surgical ground, their efficacy in the short and long term should be still demonstrated.

Other devices are expected to be more effective, but their implantation may be technically more demanding, with a consequent lack of reproducibility.

Recently, direct annuloplasty is becoming available. Direct mitral valve annuloplasty repair is a very promising approach for TMVR, as it closely reproduces a gold-standard surgical method. The Cardioband (ValtechCardio Inc., Or Yehuda Israel) is the closest transcatheter device to a surgical prosthetic ring.²⁰ It is delivered from a transeptal approach, and the implant is performed on the atrial side of the mitral annulus. A surgical-like adjustable Dacron band is implanted from trigone to trigone, by means of multiple anchors. Ongoing feasibility trial is enrolling high-risk patients with FMR. Initial clinical data are promising, showing that Cardioband implantation is associated with significant reduction of mitral regurgitation, increased leaflet coaptation surface and consistent septo-lateral annular dimension.²¹ Recently, the device has been granted the CE mark, and it is available for clinical use in Europe.

Promising initial clinical results have been showed also with the Mitralign device (Mitralign Inc., Tewksbury, MA USA) that performs selective applications of the mitral annulus by deploying couples of transannular pledgets in the annulus. Patient enrolment in the CE mark trial is completed, but the device is still not available for clinical use (Martinez-Clark P. MITRALIGN IN FUNCTIONAL MITRAL REGURGITATION, Paris, EuroPCR 2014).

The Accucinch System (Guided Delivery Systems, Santa Clara, CA USA) is another direct annuloplasty device that uses the retrograde transventricular approach. A series of anchors are implanted beneath the mitral valve in the basilar LV. These anchors are connected by a nitinol wire in which tethering the cord cinches the basal LV and mitral annulus. The Accucinch System also causes remodelling of the basal portion of the LV and is unique in this respect.

Today, the main concern about mitral direct annuloplasty repair is that these procedures are technically very challenging, and this aspect could limit their rapid and effective adoption in the real world.

TMVR armamentarium also includes artificial chordae implantation, which are anchored to the LV apex to restore mitral valve competency (NeoChord Inc., Eden Prairie, Minnesota, USA). This procedure is performed through a transapical, off-pump, beating heart approach.

It has been used successfully in several patients, with the evidence of a learning curve. Long-term durability of this approach remains an issue.

Different ventricular or atrial remodelling devices complete the wide spectrum of TMVR technologies, but limited clinical data are today available for these approaches.²²

Limitations of repair and replacement: durability and need for anticoagulation

Durability of a tissue valve in mitral position is a major concern in surgery, especially in younger patients. So far, patients who undergo transcatheter mitral procedures are mainly high-risk, elderly or inoperable patients. In this context, durability of a transcatheter mitral prosthesis has represented a minor issue.

However, if transcatheter procedures aim to become a realistic alternative to surgery and expand indications to a lower risk population, durability of the device should be considered as a priority. The degeneration process of a biological prosthesis starts in average 5 years after operation in mitral position.⁹ Durability of biological prosthesis in mitral position is largely suboptimal in patients younger than 65 years,²³ mainly due to the high-pressure gradient between left atrium and LV.

Durability is a major issue also for mitral repair. Four-year results of the EVEREST II trial²⁴ showed that when acute procedural result is optimal, transcatheter mitral repair is durable. However, in case of mitral regurgitation persistence or recurrence after mitral repair, outcomes are poor, with reduced survival, increased risk of cardiac events and reduced likelihood of reverse remodelling.²⁵

Acute successful reduction of mitral regurgitation is fundamental to provide durable results in TMVR, suggesting that patients eligible for reparative procedures should be treated only in high-volume high-experienced centres, exactly as for reparative surgery.²⁶

All the patients who undergo TMVI would probably require long-term anticoagulation. Although at the moment no long-term data are available, it is likely that duration of anticoagulation will be lifelong. Chronic anticoagulation is associated with increased risk of haemorrhagic and thrombotic events, suggesting that patients with an artificial prosthetic valve in mitral position, differently from patients receiving valve repair, never have a restored expectancy of life compared with the age-matched population.¹⁰ Risk of prosthetic valve endocarditis is another issue. The patients treated with a mitral prosthesis are not really cured: they will change their bad-prognosis disease (mitral regurgitation) to another disease with a much better prognosis, which we could call 'prosthetic valve disease'. This aspect cannot be accepted if an expansion of the indications towards a lower risk population is advocated.

Towards a prognostic approach: safety rather than efficacy is the key for a surgical-like early indication with transcatheter mitral procedures

Many physicians consider transcatheter mitral techniques as the natural and inevitable evolution of modern mitral surgery. However, if transcatheter procedures aim to expand indications to a lower risk population, interventional indications will inevitably move towards a prognostic rather than palliative approach.

Current evidence suggests that when patients are treated in a too advanced clinical status, outcomes become poor and transcatheter mitral procedures are unable to modify the clinical course of the disease and to influence the prognosis.²⁷ Surgical experience with mitral valve intervention showed that early timing is crucial to achieve a substantial prognostic benefit: restore expectancy of life in DMR patients and obtain reverse remodelling in FMR patients.⁷ It is a matter of fact that the impact of the intervention will be much more efficient when executed early in the clinical course of the disease. Several issues raise concerns on the role of TMVI in patients in their early stage of the disease. Only a very well tolerated procedure can justify a transcatheter therapy as a first-line option. If we consider safety and early indication, repair should be preferred to TMVI due to the lack of the consequences of a prosthesis (including anticoagulant therapy, risk of structural valve deterioration and risk of infection), which can't be accepted if a prognostic and early therapeutic approach is assumed.

When considering an early indication, the safety of a procedure plays a much more important role than the efficacy. A typical example is cardiac resynchronization therapy (CRT): a widely accepted heart failure therapy, even if clinical efficacy is achieved only in about 60–70% of the cases.²⁸ Patients are referred for CRT, even if there is a 30–40% rate of nonresponders, because it is conceived as a well tolerated therapy and patients are sent to get a chance of improvement, without much risk. Therefore, safety is the key for early indication, and it will be in the future the first indicator of success for a procedure.

The complementary role of repair and replacement: the Mitral Toolbox

TMVI has the potential to be technically simpler and more versatile as compared with repair; in addition, TMVI will be more predictable in terms of mitral regurgitation reduction. Durability, safety and distortion of the physiology remain major concerns. Repair is more complex, and it is applicable only in selected patients, with a less predictable mitral regurgitation reduction. On the other hand, durability is very good in many patients, if procedural success is achieved. Impact on physiology is minimal, and safety profile is higher. Therefore, TMVR may in the near future aspire to provide early

indication in lower risk patients, according to a surgical-like prognostic approach.

TMVI will be complementary therapeutic option for a great number of patients, especially in an advanced phase of the disease, with both DMR and FMR, who are not amenable for valve repair. Transcatheter mitral repair should remain the first-line therapy whenever feasible and will be mainly performed in highly experienced centres. Careful patient selection will be extremely important to define the complementary clinical role of TMVI and TMVR.

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